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Facile One-pot Synthesis of Naphthoquinone–1,3-Dithioles via 2,3-Dichloro-1,4-naphthoquinone and Amines Involving CS_2

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An efficient, simple, and facile one-pot approach of synthesizing naphthoquinone–1,3-dithioles via 2,3-dichloro-1,4-naphthoquinone and amines involving CS_2 was investigated. Both amino acid esters and aliphatic primary amines were applicable to this reaction and gave the corresponding heterocycles in good yields through the two-step sulfur-attack process.

In recent years, maximizing synthetic efficiency while at the same time minimizing unnecessary synthetic steps is a very important and extremely powerful tool offering a straightforward route to generate complexity and diversity in a single operation to construct numerous biologically active molecules.[1] Compounds containing the sulfur heterocycles have shown a wide range of pharmacological activities, found in common structural scaffolds in natural products and bioactive molecules.[2] Additionally, derivatives of sulfur heterocycles such as 1,3-dithioles have been widely explored as new materials because of their superconducting, optical, and electronic switching properties.[3] In particular, tetrathiafulvalenes (TTFs) (Figure 1) are the most successful class of heterocycles in terms of creating highly conducting and superconducting organic crystalline materials,[4] and TTF–quinones systems constitute a promising field of applications due to the interesting optoelectronic properties they exhibiting.[5]

At the same time, the quinone structure is common in numerous natural products[6] and important pharmacophores.[7] Furthermore, a number of quinone structures, particularly, heterocyclic quinones are associated with anticancer,[8] antibacterial,[9] antimalarial,[10] and fungicide activities,[11] and antiparasitic agents.[12]

There are few protocols for the corresponding synthesis of heterocyclic quinone derivatives involving C–S bond formation, Compared to the new C–N and C–O bond-forming technologies, despite the importance of sulfur-containing compounds. During the past decades, several examples of synthesis of naphthoquinone–1,3-dithioles(naphtho[2,3-d][1,3]dithiole-4,9-quinones) had been reported via 2,3-dichloro-1,4-naphthoquinone and 1,1-dithiolate, which was prepared by amine and CS_2.[13] Herein, we investigated an efficient, simple, and facile one-pot approach of synthesizing the naphthoquinone–1,3-dithioles via 2,3-dichloro-1,4-naphthoquinone and amines involving CS_2.

In order to synthesize the sulfur-containing heterocyclic compounds, our initial investigations were focused on examining the feasibility of the reaction of 2,3-dichloro-1,4-naphthoquinone (**1**) and phenylalanine ethyl ester hydrochloride (**2a**) with CS_2 (**3**) and optimizing the reaction conditions for application to synthesize a variety of naphthoquinone–1,3-dithiole derivatives. To our delight, the desired product **4a** was obtained in 56.5% yield, and 40.5% of **1** was recycled (Table 1, Entry 1). Encouraged by these results, we then started to optimize the reaction conditions to make sure that the 2,3-dichloro-1,4-naphthoquinone (**1**) consumed up and improve the chemical yield. As the quantity of **2a** was up to 2 equiv, the yield of **4a** increased only slightly (Table 1, Entry 2). Several means had been tried to make sure that **1** consumed up, but the results were all unsatisfactory due to the volatility of CS_2 as the temperature increased (Table 1, Entries 3 and 4). Excitingly, the yield of **4a** had significantly increased with Et_3N increased (Table 1, Entries 1, 5, and 6). With the optimized conditions (Table 1, Entry 6), the corresponding product **4a** was obtained in 82.3% yield.

With the optimized reaction conditions in hand, we investigated the substrate scope for this reaction (Tables 2 and 3). As highlighted in Table 2, a variety of amino acid ester hydrochlorides **2a**–**2h** could react efficiently with 2,3-dichloro-

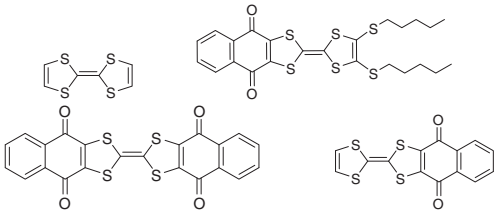
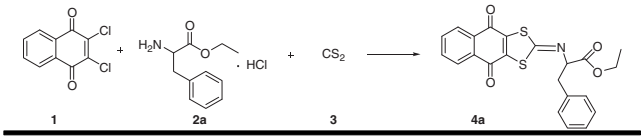


Figure 1. Several TTFs molecules.

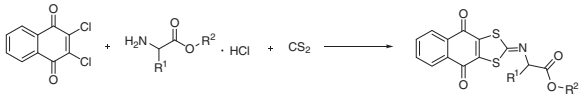
Table 1. Optimization between 2,3-dichloro-1,4-naphthoquinone (**1**), phenylalanine ethyl ester hydrochloride (**2a**), and CS_2 (**3**)

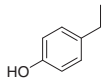
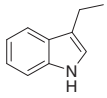


Entry[a]	**1:2a:3**	Temperature /°C	Solvent	Base (equiv)	Yield /%[b]	**1**
1	1:1.2:3	0	CH_2Cl_2	Et_3N (1.2)	56.5	40.5
2	1:2:3	0	CH_2Cl_2	Et_3N (2.0)	60.1	35.2
3	1:1.2:3	R.T.	CH_2Cl_2	Et_3N (1.2)	40.5	51.2
4	1:1.2:3	40	CH_2Cl_2	Et_3N (1.2)	35.6	53.5
5	1:1.2:3	0	CH_2Cl_2	Et_3N (2.0)	70.5	18.1
6	1:1.2:3	0	CH_2Cl_2	Et_3N (3.2)	82.3	—

[a]Reaction conditions: the mixture of **1a** (1.0 mmol), **2a** (1.2–2.0 mmol), **3** (3 mmol), Et_3N (1.2–3.2 mmol), and solvent (5.0 mL) was stirred for 2.5 h under corresponding temperature. [b]Yield of the isolated product.

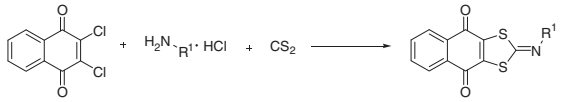
Table 2. Extending scopes using different amino acid ester hydrochlorides



Entry	2	R^1	R^2	4	Yield /%
1[a]	**2a**	$PhCH_2$–	CH_3CH_2–	**4a**	82.3
2	**2b**	$(CH_3)_2CH$–	CH_3–	**4b**	72.8
3	**2c**	H–	CH_3CH_2–	**4c**	52.3
4	**2d**	H–	CH_3–	**4d**	46.2
5	**2e**	$(CH_3)_2CH$–	CH_3CH_2–	**4e**	70.0
6	**2f**	CH_3–	CH_3CH_2–	**4f**	73.2
7	**2g**		CH_3CH_2–	**4g**	66.9
8	**2h**		CH_3CH_2–	**4h**	75.0

[a]See ref 14 for details of experimental procedure.

Table 3. Extending scopes using different primary amine hydrochlorides



Entry	2	R^1	4	Yield /%
1	**2i**	CH_3–	**4i**	78.2
2	**2j**	CH_3CH_2–	**4j**	83.6
3	**2k**	$CH_3CH_2CH_2$–	**4k**	89.3
4	**2l**	$(CH_3)_2CH$–	**4l**	58.8
5	**2m**	$CH_3CH_2CH_2CH_2$–	**4m**	73.3
6	**2n**	C_6H_{13}–	**4n**	73.1
7	**2o**	$C_{10}H_{21}$–	**4o**	78.6
8	**2p**	$C_{12}H_{25}$–	**4p**	60.2
9	**2q**	$PhCH_2$–	**4q**	60.1
10	**2r**		**4r**	48.9

1,4-naphthoquinone in the presence of CS_2, and the corresponding products could be obtained in good to excellent yields (Table 2, Entries 1–8). Unfortunately, lower yields of **4c** and **4d** were obtained: 52.3 and 46.2%, respectively; the reason may be that the side reaction of urea was increased due to the small steric effect of glycine ester (Table 2, Entries 3 and 4). The structure of **4a** was determined by X-ray crystal analysis (Figure 2).[16]

In order to further extend the applicability of this reaction, we also investigated the aliphatic primary amines in this reaction; the results are summarized in Table 3. Propylamine was used in order to establish the full scope of this interesting reaction at first. Unfortunately, the corresponding product **4k** was only obtained in 68.5% yield when propylamine was used

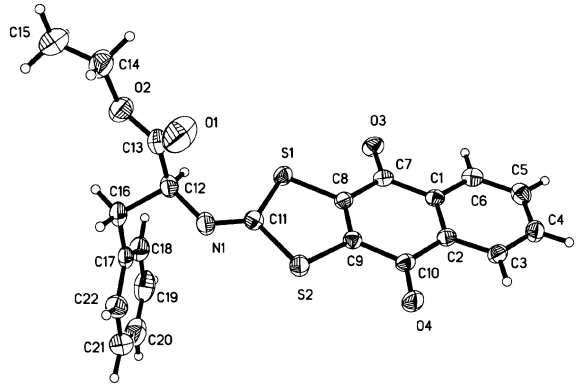
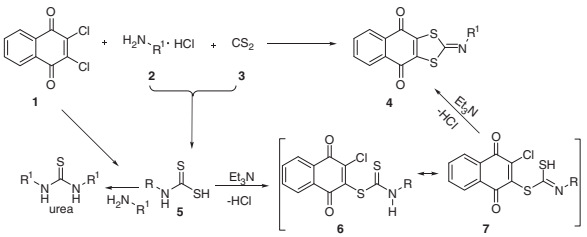


Figure 2. ORTEP drawing of **4a**.



Scheme 1. Proposed reaction pathway.

as the reactant under the same condition as above and urea was used as the by-product with the side reaction of CS_2 and amine. Excitingly, the yield of **4k** improved to 89.3% when propylamine hydrochloride and Et_3N were employed (Table 3, Entry 3). The different primary amine hydrochlorides **2i**–**2r** bearing the various linear and branched chain alkyl groups, benzyl group all yielded the corresponding products in 48.9–89.3% yields (Table 3, Entries 1–10). Cyclohexylamine was obtained in 48.9% yield because of the low reactivity due to the steric hindrance of cyclohexylamine.

According to these results, a possible mechanism for this reaction was proposed in Scheme 1. First, the intermediate **5** was afforded by the addition of amine to CS_2.[17] Subsequently, the initial addition product **6** was obtained as the sulfur of intermediate **5** attacked **1** and further to its tautomer **7**, and then, the product **4** was obtained through the same sulfur-attack procedure. At the same time, the intermediate **5** added to the amine and turned into the by-product urea.[18]

In summary, we have developed an efficient and facile one-pot approach of synthesizing naphthoquinone–1,3-dithioles via 2,3-dichloro-1,4-naphthoquinone and amines involving CS_2. Fatty amines and amino acid ester all gave the corresponding product in good yield. This reaction will stimulate the synthetic applications of sulfur-containing heterocycles by employing these inexpensive reagents of CS_2. Therefore, the potential applications of these compounds will be interesting in pharmaceutical and material research. Further related investigation on the synthesis and applications will be ongoing in our laboratory.

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14 General procedure for synthesis of ethyl 2-(4,9-dioxo-4,9-dihydronaphtho[2,3-*d*][1,3]dithiol-2-imino)-3-phenylpropanoate (**4a**):[15] A mixture of 2,3-dichloro-1,4-naphthoquinone (**1a**, 1.0 mmol, 0.226 g, 1.0 equiv), phenylalanine ethyl ester hydrochloride (**2a**, 1.2 mmol, 0.276 g, 1.2 equiv), CS_2 (**3a**, 5 mmol, 0.381 g, 5.0 equiv), triethylamine (3.2 mmol, 0.324 g, 3.2 equiv) in CH_2Cl_2 (5.0 mL),was stirred at 0 °C under air condition for 2.5 h, determined by GC-MS and TLC. The solvent was removed under vacuum and the resulting crude product was purified by chromatography on silica gel eluted using CH_2Cl_2 as the eluent to afford the desired product **4a** as red solid (0.348 g, yield 82.3%, mp: 149–150 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.12–8.08 (m, 2H), 7.78–7.74 (m, 2H), 7.31–7.28 (m, 2H), 7.26–7.20 (m, 3H), 4.22 (q, $J = 7.0$ Hz, 2H), 3.93 (dd, $J_1 = 5.5$ Hz, $J_2 = 8.5$ Hz, 1H), 3.32 (dd, $J_1 = 5.0$ Hz, $J_2 = 13.5$ Hz, 1H), 3.14 (dd, $J_1 = 8.0$ Hz, $J_2 = 13.0$ Hz, 1H), 1.26 (t, $J = 8.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.1, 175.5, 169.6, 160.7, 143.6, 142.6, 136.6, 134.3 (2C), 132.0, 131.9, 129.6 (2C), 128.5 (2C), 127.1 (2C), 127.0, 73.4, 61.6, 39.1, 14.1; EI-MS m/z: 424.18 $[M + H]^+$; Anal. Calcd for $C_{18}H_{17}NO_4S_2$: C, 62.10; H, 4.50; N, 3.29; S, 15.07%. Found: C, 62.39; H, 3.97; N, 3.17; S, 14.69%.

15 Experimental procedures, characterizations, and NMR spectra of compound **4** and X-ray crystal structure of compound **4a** are in Supporting Information. Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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